Review

Natural Product Communications
May 2019: 1–20

DOI: 10.1177/1934578X19845813
journals.sagepub.com/home/npx

SAGE

Naturally Occurring Homoisoflavonoids: Phytochemistry, Biological Activities, and Synthesis (Part II)

Berhanu M. Abegaz[1,2] and Henok H. Kinfe[2]

Abstract

This review documents all the new homoisoflavonoids (HIFs) that have been reported since 2007, whose total number has grown from 159 in 2007 to 295 at the present time. This review contains their structures, biological sources, plant parts they are obtained from, and, if reported, their optical rotations and melting points. The same classification is followed as an earlier review to ease reference to both reviews. This review takes note of the recent revision of plant families that were known to contain HIFs that have now been merged into one big family, Asparagaceae. Homoisoflavonoids also occur in Fabaceae and others. Two taxa, *Ophiopogoan japonicus* (Asparagaceae) and *Caesalpinia sappan* (Fabaceae), have been the source of many HIFs. These are briefly summarized. The biological properties of HIFs are also reviewed under the topics such as antioxidant, anti-inflammatory, antimicrobial, antidiabetic, and cytotoxic. The review also surveys the total synthesis of natural HIFs. All new compounds are classified and tabulated following the same style as the previous review.

Dedicated to Professor Andrew Paul Krapcho on the occasion of his 87th Birthday.

Keywords

homoisoflavonoids, 3-benzyl-chroman-4-ones, 3-benzylflavans, scillascillins, flavonoids

Received: December 2nd, 2018; Accepted: January 22nd, 2019.

Homoisoflavonoids represent a subclass of the larger family of flavonoids (**1**) that are uniquely characterized by having one more carbon (C-9) than the regular flavonoids in their 16-carbon skeleton (**2**) (Figure 1). Labeling studies[1,2] have provided evidence to support the biogenetic hypothesis that they are biosynthesized from a 15-carbon flavonoid precursor.

This review is a follow-up of an earlier one in 2007[3] listing the 159 compounds which were known then. The total number of naturally occurring HIFs has now reached 295 and this review documents the new metabolites belonging to this class that have been discovered since then. This review is based on a survey of publications that have appeared in Scopus and the Science Citation Index during the period 2007 to 2018.

Five important review publications relevant to the field of HIFs have appeared during this review period. The first is a review of the chemical structures, plant origins, ethnobotany, and biological activities of homoisoflavanones,[4] listing 129 compounds. This number is less than the 159 recorded in the earlier review, because the authors focused only on metabolites having a selected number of structural types under this class. The second is a review of HIFs and their pharmacological activities.[5] This lists 240 naturally occurring HIFs and contains a comprehensive listing of all natural HIFs known at the time of the review (2014). The coverage is limited to recording all the metabolites and discusses pharmacological properties. The third review is devoted to one homoisoflavonoid, namely, brazilin.[6] Brazilin (**3**) (Figure 2) is the major and most biologically active of the 3 HIFs found in the heartwood of *Caesalpinia sappan*. The review documents the scientific evidence supporting the folkloric uses of brazilin as an antioxidant and antibacterial, with anti-inflammatory, antiphotoaging, hypoglycemic, vasorelaxant, hepatoprotective, and antiacne activity (more on this compound, later). The fourth is a phytochemical, ethnomedicinal, and pharmacological review of the taxon *Ophiopogon japonicus,*

[1] Stellenbosch Institute for Advanced Study, Wallenberg Research Centre at Stellenbosch University, South Africa
[2] Department of Chemistry, Center of Synthesis and Catalysis, University of Johannesburg, South Africa

Corresponding Author:
Berhanu M. Abegaz, Stellenbosch Institute for Advanced Study, Wallenberg Research Centre at Stellenbosch University, Stellenbosch 7600, South Africa.
Email: babegaz@gmail.com

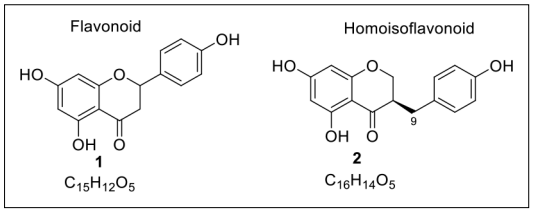


Figure 1. General scaffolds of a flavonoid and an HIF.

a functional food and commercial medicinal plant, whose biological activities are due to 3 major classes of metabolites: saponins, HIFs, and polysaccharides.[7] The published evidence summarized in this review points to the HIFs contributing to the anti-inflammatory and antioxidant properties of the medicinal plant. The fifth review is the first comprehensive report in recent times devoted to what is often referred to as Dragon's blood. This review sheds much needed light to clarify the confusion that prevailed on the source and composition of Dragon's blood which refers to red saps and resins derived from a few disparate taxa.[8] Although this multipurpose material was originally from *Dracaena* species, the review reveals that there are 4 distinct plant genera, namely *Croton* (Euphorbiaceae), *Dracaena* (Dracaenaceae, now: Asparagaceae), *Daemonorops* (Palmaceae), and *Pterocarpus* (Fabaceae) that are described in the literature as sources of Dragon's blood. Of the 4 genera, only *Dracaena cinnabari*[8] and *Dracaena cochinchinensis*[9-11] contain HIFs.

Distribution of HIFs

Many of the plant families that were known to produce HIFs, such as Anthericaceae, Liliaceae, Convallariaceae, Dracaenaceae, and Hyacinthaceae, have now been grouped under one big family, Asparagaceae (Accessed September 13, 2018 [http://www.plantsoftheworldonline.org/taxon/urn:lsid:ipni.org:names:481889-1]). So, all references to these families are recorded as Asparagaceae in this review. There are now 7 other families besides Asparagaceae that are known to produce HIFs: Amarillidaceae, Araliaceae, Fabaceae, Orchidaceae, Polygonaceae, Portolucaceae, Rosaceae, Meliaceae, Polypodiaceae, and Similacaceae. By far the majority of HIFs is derived from the family Asparagaceae, a much lesser number from Fabaceae, and 1 or 2 genera belonging to the other families. Many names of species have also changed. For example, *C. sappan* L. is considered as the synonym of *Biancaea sappan* (L.) Tod. and taxonomic information for this taxon from Kew's http://www.plantsoftheworldonline.org/ (Accessed September 13, 2018 [http://www.plantsoftheworldonline.org/taxon/urn:lsid:ipni.org:names:481889-1]) is given using the latter. To avoid confusion, we have retained the earlier names at the taxon level.

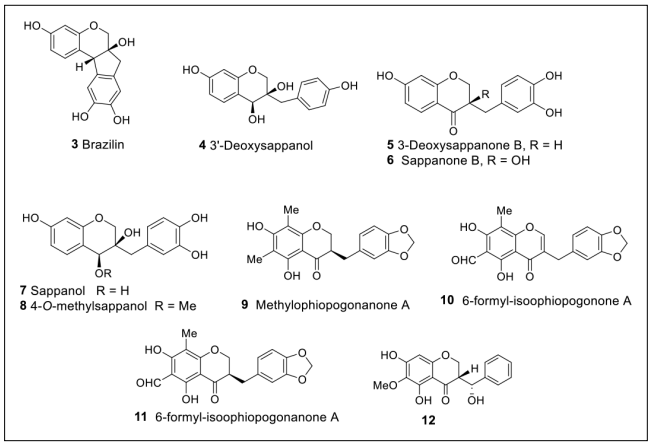


Figure 2. Examples of HIFs.

Advances in Extraction and Separation Methods

One of the major challenges in the study of secondary metabolites has always been their purification and isolation from complex plant extracts.

The usual methods involve silica gel chromatography, which inevitably results in the irreversible adsorption of some of the components and in some cases even a change in the integrity of the metabolites. In this regard, there have been some advances reported during the period under review of gentler methods of isolation of HIFs. Xu et al have reported the successful separation of 4 HIFs from *C. sappan* by high-speed counter-current chromatography (HSCCC).[12] The crude extract of *C. sappan* was fractionated by HSCCC using a 2-phase solvent system consisting of chloroform-methanol-water (4:3:2, v/v/v). The separation conditions were: flow rate, 1.0 mL/min; revolution speed, 900 rpm; detection wavelength, 280 nm; separation temperature, 25°C; sample size, 120 mg crude sample dissolved in a mixture of the upper and lower phases (10 mL each). The retention of the stationary phase was 83%. This method delivered 5 mg of 3′-deoxysappanol (**4**), 8 mg of 3-deoxysappanone (**5**) B, 20 mg of 4-*O*-methylsappanol (**8**), and 18 mg of brazilin (**3**) in one step from 120 mg of an ethyl acetate extracted fraction of *C. sappan* (Figure 2).

In another instance Ma et al[13] reported a method that combines supercritical fluid extraction and HSCCC to extract and purify HIFs from *O. japonicus*. Thus, in a single operation, 140 mg crude extracts were separated and yielded 15.3 mg of methylophiopogonanone A (**9**) (96.9% purity), 4.1 mg of 6-formyl-isoophiopogonone A (**10**) (98.3% purity), and 13.5 mg of 6-formyl-isoophiopogonanone A (**11**) (97.3% purity) (Figure 2).

Uddin et al have reported a centrifugal partition chromatography (CPC)-based one-step isolation of sappanol (**7**) and brazilin (**3**) from *C. sappan*.[14] Using the solvent system, ethyl acetate:acetonitrile:water, 1:1:2, v/v, the ethyl

acetate-soluble material (350 mg) was subjected to CPC to yield the 2 HIFs.

Theoretical Studies on HIFs

As this class of compounds are more explored in terms of their structural diversity and biological properties, it becomes important to obtain a deeper insight into their properties through theoretical studies. We have observed such studies during the last decade that address the electronic distribution of HIFs. Discrete Fourier Transform (DFT) calculations of nuclear magnetic shielding for optimized geometries of HIFs show good correlations with experimentally measured values.[15]

More effective chiroptical methods are now available[16,17] to solve absolute configuration issues. These involve combinations of electronic and vibrational chiroptical spectroscopic methods and interpretations of measured spectra with the aid of density functional theory calculations.

These methods[18] were employed in determining the absolute configuration of 5,7-dihydroxy-6-methoxy-3-(9-hydroxy-phenylmethyl)-chroman-4-one (**12**). This substance had been isolated from the dry leaves of *Polygonum ferrugineum*,[19] now renamed as *Persicaria ferruginea* (Wedd.) Soják (Polygonaceae), and from *Polygonum senegalense*[20] (*Persicaria senegalense* (Meisn.) Soják), with widely differing optical rotation values. The former group reported $[\alpha]_D$ −8.67 in dichloromethane, while the latter group reported a value of +41 in methanol. Interestingly, a third group[21] had isolated the same substance from *Polygonum libatum* with $[\alpha]_D$ of zero and presumed the isolate to be a racemic mixture. Batista et al[18] investigated and first made the unexpected discovery that the differences were a result of the solvents used for the measurements and not due to different ratios of enantiomers. The specific rotation of **12** in chloroform was +44, which is much closer to the value obtained in methanol than to that measured in dichloromethane. These authors used this observation to caution on the risks of comparing optical rotation values in different conditions, even when apparently similar solvents are used. The absolute configuration of **12** was unambiguously assigned as 3*R*,9*R* by means of a combination of chiroptical methods and theoretical calculations.

Ophiopogon japonicus and C. sappan

Ophiopogon japonicus (Thunb.) Ker Gawl. and *C. sappan* (now called *Biancaea sappan* (L.) Tod. have been the subject of intense investigations during the last 10 years. *Ophiopogon japonicus* is an important medicinal plant which is native to Central and South China to Vietnam, temperate East Asia to the Philippines and has been introduced to some areas of central South America (Argentina, Uruguay, and Paraguay). Besides its use in the treatment of a variety of ailments, it is considered as a functional food in China and other East Asian countries. The main active ingredients are believed to be steroidal compounds and HIFs.[7] The Chen review[7] of this plant records 36 HIFs reported from *O. japonicus*. Further metabolites have been reported since then. Thus, 18 new HIF metabolites have been reported from this taxon since our last review, homoisopogon B-D (**14, 18, 19**), (3*R*)-2,3-dihydro-7-hydroxy-5-methoxy-3-(4′-methoxybenzyl)-6,8-dimethyl-4H-chromen-4-one(**39**),8-formylophiopogonanone B (**42**), ophiopogonanone G (**61**), homoisopogon A (**62**), (3*R*)-3-(1,3-benzodioxol-5-ylmethyl)-2,3-dihydro-7-hydroxy-5-methoxy-6- methyl-4H-chromen-4-one (**63**), (3*R*)-3-(1,3-benzodioxol-5-ylmethyl)-2,3-dihydro-7-hydroxy-5-methoxy-6,8-dimethyl-4H- chromen-4-one (**70**), ophiopogoside A (**73**), ophiopogoside B (**75**), 4′-*O*-demethylophiopogonanone E (**81**), 5,7,2′,3′-tetrahydroxy-6-methyl-8-methoxy-3-(4′-methoxybenzyl)chroman-4-one,(**84**),ophiopogonanoneH(**98**),6-formylophiopogonone B (**128**) 8-formyl-7-hydroxy-5,4′-dimethoxy-6-methylhomoisoflavone (**129**), ophiopogonone D (**130**), and ophiopogonone E (**131**).[22-28]

For *C. sappan,* the native range is the Indian subcontinent to Indo-China. It has been introduced to Nigeria, the Congo, Mozambique, Tanzania, and Uganda in Africa (Accessed September 13, 2018 [http://www.plantsoftheworldonline.org/taxon/urn:lsid:ipni.org:names:481889-1]). The heart wood of *C. sappan* is the most used part and studies have shown that the main homoisoflavonoid ingredient of the heartwood of this plant is brazilin (**3**), which is responsible for several of the observed biological activities, which include cytotoxic, antitumor, antimicrobial, antiviral, immunostimulant, and other properties. This plant has been the subject of several studies which have resulted in the identification of many new HIFs including the first report of a $\Delta^{3,4}$-unsaturated homoisoflavan from a natural source (**20**), 3′-deoxy-4-*O*-methylepisappanol (**28**), (*3R,4S*)-3,7-dihydroxy-3-(3′-methoxy-4′-hydroxybenzyl)-4-ethoxychroman (caesalpiniaphenol F, **29**), (3*S*,4*R*)-3,7,2′,3′-tetrahydroxy-3,4-dihydro-9H-indeno[6,5 c] chromene (caesalpiniaphenol E) (**142**),[29] caesalpinophenols G (**84**) and H (**146**), (*3R*)-3,7-dihydroxy-3-(4′-hydroxy-3′-methoxybenzyl)-chroman-4-one (**85**),[30] 7,10,11-trihydroxydracaenone (**143**), epicaesalpin J (**144**),[31] caesappin A (**145**), and caesappin B (**150**).[32]

Novel Structures Containing the HIF Skeleton

Novel structures that have been reported during this period will be summarized hereunder. In the earlier review[3] a few HIFs with attachment of sugar units were reported. A 5-*O*-glucoside, 5-*O*-rutinoside, and a 5-*O*-neohesperoside were listed, which were linked to 3-hydroxy-3-benzylchroman-4-ones. These were isolated from *Ornithogalum caudatum*. During the current review period a few more glycosides have been reported. Simple 7-*O*-glucosides (**74** and **75**) were reported from *O. japonicus*.[26] Two disaccharide glycosides

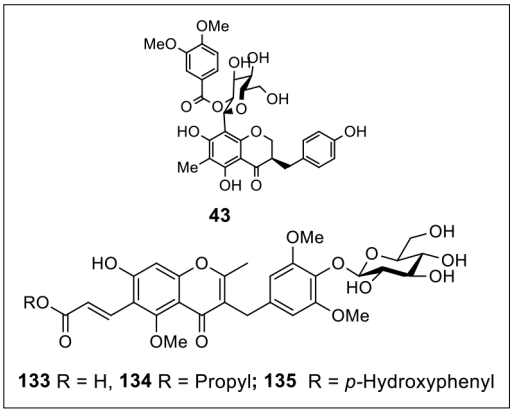


Figure 3. Glycosylated HIFs.

of benzylchroman-4-ones (**44** and **45**) were also reported from *Ledebouria floribunda*.[33] A slightly more complex glycoside, (3*R*)-5,7-dihydroxy-8-(2″-*O*-veratroyl-β-D-glucopyranosyl)-3-(4′-hydroxyphenyl)-6-methylchroman-4-one (**43**) (Figure 3) has been reported from the Araliaceae plant *Acanthopanax brachypus*.[34]

Furthermore, a biogenetically intriguing set of 3 homoisoflavonoid glycosides (**133, 134,** and **135**) (Figure 3) has been reported from *Prunus domestica* belonging to the Rosaceae family.[35] What is distinct about these 3 compounds is the unique carbon framework which has a methyl substituent at C-2, a $\Delta^{2,3}$-unsaturation, and glucosylation of a sterically crowded C-4′-hydroxyl group of ring β-propenoic acid, whose β-carbon is attached to C-6, is seen to extend further

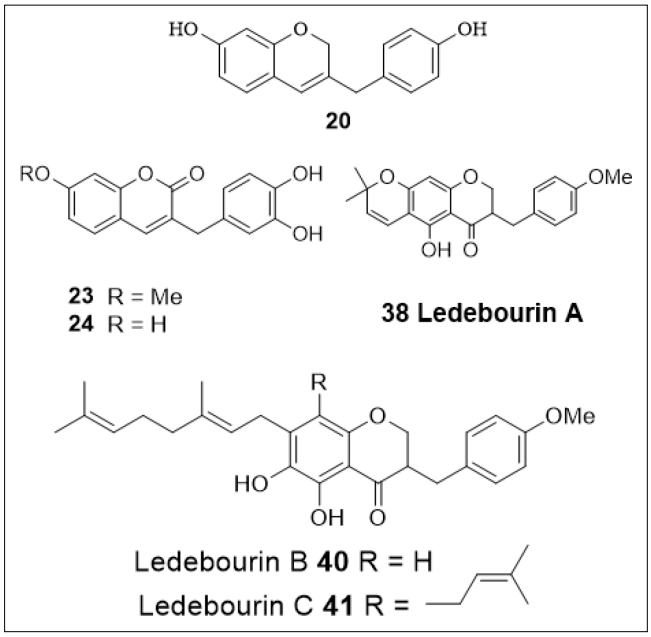


Figure 4. Examples of unusual HIFs.

the homoisoflavonoid carbon framework. Further elaboration takes place where esterification with propyl alcohol gives **134** and with hydroquinone **135**. It is to be noted that these unusual glycosides are found in the 2 families, Araliaceae and Rosaceae, where HIFs are unknown or extremely rare. The compounds **133** to **135** showed potent inhibitory activity against α-glucosidase and this is further discussed in a later section on antidiabetic properties of HIFs.

Although prenylated and geranylated flavonoids are very common in certain families of plants, compounds **38**, **40**, and **41** (Figure 4) are the first examples of prenylated HIFs. These unusual compounds were reported from the bulbs of *L. floribunda*.[36]

Zhao et al[37] reported the isolation of the 3-benzylchromen **20** (Figure 4) from *C. sappan* and observed that this may have been the first natural product possessing a double bond located at C-3 and C-4 of a homoisoflavan system. In 2016 came a further report on the isolation of 3 more similar $\Delta^{3,4}$-unsaturated compounds, but with additional hydroxy and methoxy substituents[38,39] from *Caesalpina spinosa* and *Herreria montevidensis*, respectively. Interestingly, He et al also reported 2 more compounds **23** and **24** from the same plant, which contain a carbonyl group at C-2. This compound was identified as a 3-benzyl coumarin, although it can also be characterized as an oxidized homoisoflavonoid. The natural occurrence of **23** and **24** (Figure 4) has a special biogenetic significance and may indicate a new biosynthetic route to coumarins that have not been realized before.

In 2014 Wang and coworkers isolated caesappin A (**145**) together with caesappin B (**146**), where the latter is most probably the precursor of **146** (Wang et al., 2014). These compounds are unusual in that there has been a rearrangement of the carbon framework (cf. epihematoxylol B **147** (Lin et al., 2014a)) for which these workers propose the mechanism depicted in Scheme 5 showing how they may be biosynthesized in the plant. Scheme 5. Biogenetic scheme to caesappin A (**145**).

Classification of HIFs

This report is prepared by following the classification of HIFs proposed in the 2007 review[3] and carefully building on it to update the total number of HIFs that is known from natural sources to date. This will enable readers to consult the 2 reviews and get a full and broader coverage of the subject. Therefore, the HIFs are classified into 5 major groups A to E as restated below and depicted in Figure 5.

The first group, A (Table 1), is based on the 3-benzylflavan skeleton, with a new subclass containing $\Delta^{3,4}$-unsaturation and 3,4-dioxygenation.

The second group, B (Table 2), consists of the 3-benzylchroman-4-ones. The majority of the recently discovered HIFs belongs to this class. Also included in this section are

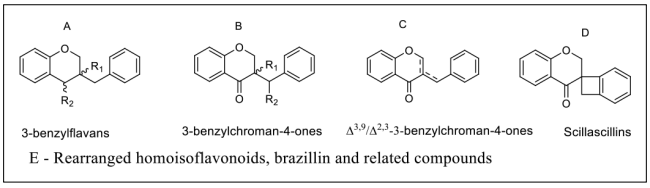


Figure 5. The five groups (A-E) of homoisoflavoids.

the 3-hydroxy derivatives (Table 3), which are fewer, with just 2 compounds **102** and **103** having 9-hydroxy substituents.

Group C compounds have the $\Delta^{3,9}$ with either *E* or *Z* stereochemistry at the $\Delta^{3,9}$-double bond and derivatives (Table 4). Many HIFs in this subgroup belong to the *E* series. The observation made in the previous review where the $\Delta^{2,3}$[3] unsaturated HIFs were largely restricted to the genus *Ophiopogon* is repeated once again.[24-26,28,35]

Group D is the scillascillins (Table 5). Only 6 HIFs in this class (**136-141**) are reported in this period.

Group E contains the rearranged polycyclic HIFs (Figure 6). Ten HIFs (**130-138**) with 5 carbon skeletons have been reported from 2 species, *C. sappan* and *Haematoxylon campechianumi.*

Biological Activities of HIFs

Pharmacological Properties of Brazilin

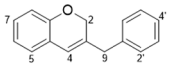
A recent review[6] has dealt with the pharmacological activities of the homoisoflavonoid brazilin. This review states: *Brazilin is the safe natural compound having potential to develop as a medicinal compound with application in food, beverage, cosmetics and pharmaceutical industries to screen its clinical use in modern medicine* but cautions that *more studies are needed to evaluate the potential application of brazilin as preservative and coloring agent in food processing industries*. Brazilin is reported to have a high antioxidant property (IC_{50} 8.8 µM) comparable with or better than (+)-catechin (10.2 µM). It has also been found to be effective against drug-resistant Gram-positive bacteria including MRSA, vancomycin-resistant enterococci, and multi-drug-resistant *Burkholderia cepacian*. Brazilin showed antibacterial activity with a Minimum inhibitory concentration of 0.50 mg/mL. The 50% inhibitory concentration (IC_{50}) for lipase inhibition was lowest for brazilin (6 µM), which showed strong inhibition compared with chloramphenicol (677 µM, positive control).[80] Experimental evidence is outlined in the Nirmal review supporting the beneficial hypoglycemic role of brazilin by enhancing glucose metabolism in adipose tissue, by inhibiting protein kinase C and insulin receptors serine kinase, and by inducing glucose transport in isolated rat epididymal adipocytes, including details on its mechanism of action.[6] The vasorelaxing property of brazilin has also been documented. Brazilin relaxed phenylephirine-induced vasoconstriction and increased cGMP in isolated rat aorta. More recently, brazilin is reported to increase the life span of the nematode worm *Caenorhabditis elegans*. The mean life of 12.3 ± 0.4 days was increased to 14.5 ± 0.4 days when the worms were fed 100 µM brazilin.[81]

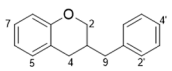
Antioxidant and Anti-Inflammatory Properties

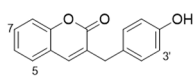
The antioxidant and anti-inflammatory properties of several HIFs have been reported using the simple 2,2-diphenyl-1-picrylhydrazyl (DPPH) method, the inhibition of nitric oxide (NO) or the suppression of inducible nitric oxide (iNOS) synthase, inhibiting prostaglandin (PGE_2), interleukin (IL)−1b production, etc. *Ledebouria floribunda* has been identified as a source of HIFs, some with prenyl and geranyl groups and others with glycosidic linkages.[33,36] The 3 prenylated and geranylated derivatives (**38**, **40,** and **41**) are the first reports of HIFs with triple (acetate, shikimate, and mevalonate) biosynthetic pathways. These were assessed for their DPPH scavenging properties (Table 6) and were found to be either stronger or equal to the usual reference antioxidants like Butylated Hydroxytoluene (BHT) and Butylated hydroxyanisole (BHA). The expected activity due to the ortho dihydroxy groups is probably enhanced by other factors introduced by the prenyl and geranyl groups.

Calvo et al[36] also reported HIFs with sugar groups attached to the C-7 phenolic group of ring A. Their antioxidant properties have been assessed using both the DPPH scavenging as well as the β-carotene/linoleic acid system. The results showing strong antioxidant properties are shown in Table 6.

Hung et al[26] investigated the effect of HIFs on the release of the inflammatory chemokine eotaxin, stimulated by IL-4 and in combination with TNF-α in BEAS-2B cells, which mimics the in vivo conditions in bronchial allergic asthma. They investigated the ability of HIF ophiopogoside A (**62**), ophiopogoside B (**63**), and ophiopogonanone G (**72**) to regulate cytokine-induced eotaxin expression in the human bronchial epithelial cell line BEAS-2B. IL-4 stimulation (20 ng/mL) of BEAS-2B cells for 48 hours increased eotaxin production from 10.7 to 60.5 pg/mL. The HIFs at 1.0, 5.0, 10.0, and 25.0 µM significantly downregulated IL-4-induced eotaxin production in a dose-dependent manner. At a concentration of 25 µM, ophiopogoside A (**62**), ophiopogoside B (**63**), and ophiopogonanone G (**69**) reduced eotaxin production to 30.8, 28.5, and 25.5 pg/mL, respectively. It was also shown that these compounds could inhibit eotaxin production in the combination of IL-4 and TNF-α stimulation; the cells were pre-incubated with compounds **62** and **63** for 2 hours and then activated with IL-4 (10 ng/mL) and TNF-α (10 ng/mL). The BEAS-2B cells produced 28.1 pg/mL







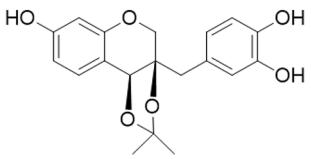


Table 1. Group A: 3-Benzylflavan (**20-22** and **26-30**), $\Delta^{3,4}$- (**13-19** and **23-26**) and 3,4-dihydroxy (**31**) derivatives

No	5	6	7	8	2′	3′	4′	5′		*Source* [Family][a], part of plant	References
13			OMe				OMe		+30 (*3R*)	*H. montevidensis* [A], root	[39]
14			OMe		OH		OMe		+23	*O. japonicus* [A], tuber	[22]
15		OH		OMe			OH		+41.5. 3*R*	*Soymida febrifuga* [M], bark	[40]
16	OMe	Me	OMe				OH		+50.7 (*3R*)	*H. montevidensis* [A], root	[39]
17	OMe	Me	OH				OH		+53.8 (*3R*)	*H. montevidensis* [A], root	[39]
18		Me	OMe		OH		OMe		+18	*O. japonicus* [A], tuber	[22]
19		Me	OH			OCH_2O			+12.5	*O. japonicus* [A], tuber	[22]
20			OH				OH		-	*C. spinosa* [F], twigs and leaves	[38]
21			OH			OH	OH		-	*C. sappan* [F], heartwood	[37]
22			OH	OMe			OH		-	*H. montevidensis* [A], root	[39]
23			OH					OH	-	*Anemarrhena asphodeloides* [A], root	[41]
24			OMe					OH	-	*C. spinosa* [F], twigs and leaves	[38]
25		OMe	OH				OH		-	*S. febrifuga* [M], bark	[40]
26		OH	OH			OH	OH		-	*O. japonicus* [PP], aerial	[42]
No	3	4	7	8	2′	3′	4′	5′	Mp, $[\alpha]_D$, *R/S*	*Source* [Family][a], part of plant	References
31									-	*C. sappan* [A], heartwood	[45]

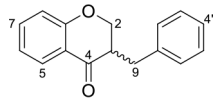
[a]A, Araliaceae; F, Fabaceae; Po, Polygonaceae; Pt, Portulacaceae; M, Meliaceae; PP, Polypodiaceae.

eotaxin in the resting stage, but, after stimulation, eotaxin production increased to 456.2 pg/mL

The anti-inflammatory properties of sappanone A (**159**) were assessed by measuring its ability to inhibit the production of NO, PGE_2, and IL-6, as well as the expression of iNOS, cyclooxygenase-2 (COX-2), and IL-6 in lipopolysaccharide (LPS)-stimulated RAW 264.7 cells.[83] These authors present evidence that leads to the conclusion that the anti-inflammatory activity of sappanone A occurs by activating the Nrf2/HO-1 pathway and by suppressing LPS-induced NF-κB activation. Their investigations have provided mechanistic details underlying the anti-inflammatory activities of sappanone A and suggest that this natural product may be useful for either the prevention or treatment of Nrf2- and/or NF-κB-dependent pathological conditions, such as inflammatory diseases.

Antibacterial, Antiviral, and Antifungal Activities

An interesting study by Jeong et al[45] presents the antiviral activities of closely related HIFs assessed against neuraminidases (NAs) on the surface of influenza viruses (A/PR/8/34 [H1N1], A/Hong Kong/8/68 [H3N2], and A/Chicken/Korea/MS96/96 [H9N2]) and confirmed by the positive control with oseltamivir (IC_{50} = 5.8 nM [H1N1], 5.6 nM [H3N2], and 1.2 nM [H9N2]). The HIFs included in these studies were brazilin (**3**), sappanone B (**6**), 3-deoxysappanone B (**5**), sappanol, episappanol, 4-*O*-methylsappanol (**8**), 3-deoxy-4-*O*-methylsappanol, 4-*O*-methylepisappanol, 4-(7-hydroxy-2,2-dimethyl-9*βH*-1,3,5-trioxa-cyclopenta[*α*] naphtalen-3*α*-methyl)-benzen-1,2-diol (**17**), 3,4,7-trihydroxy-3-benzyl-2*H*-chromene, and brazilin (**3**). Brazilin and sappanone A (**159**) were the most active with IC_{50} (μM)



32-84

Table 2. Group B-1: 3-Benzylchroman-4-Ones: Compounds **32 to 84**.

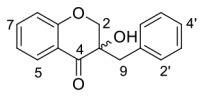
No	5	6	7	8	2′	3′	4′	5′	Mp, *R/S*, $[\alpha]_D$	*Source* [Family][a], part of plant	References
				Dioxygenated							
32	-	-	OMe				OH		3*R*, +30	*H. montevidensis* [A], root	39
				Trioxygenated							
33	OH		OH				OMe		3*S*, +6	*Urginea depressa* [A], whole plant	46
34	OH		OMe		OH		OMe		3*R*, −8	*Polygonatum sibircum* [A], rhizome	47
35	OMe		OMe		OH				160°C; +0.7	*Portulaca oleracea* [Pt], [fresh aerial]	48
36	OH	Me	OMe				OH		3*R*, −42.3	*Liriope platyphylla* [A], root	49
37	OH		OH	Me			OH		3*R*, −22.9	*Polygonatum odoratum* [A], rhizome	50
38	OH	Dimethylchromene					OMe		3*R*, −1.3	*L. floribunda* [A], bulb	36
39	OMe	Me	OH	Me			OMe		3*R*.+60.5	*O. japonicus* [A], root	23
40	OH	OH	Geranyl				OMe		3*R*, −23.7	*L. floribunda* [A], bulb	36
41	OH	OH	Geranyl	Prenyl			OMe		3*R*, −9.5	*L. floribunda* [A], bulb	36
42	OH	Me	OH	CHO			OMe		3*R*, −23	*O. japonicus* [A], root	25
43	OH	Me	OH	Gly[b]			OH		3*R*, −43.5	*A. brachypus* [Ar], root	34
44	OH		Rha-Glu[c]				OH		−22.7	*L. floribunda* [A], bulb	33
45	OH		Rha-Glu[c]				OMe		−23.7	*L. floribunda* [A], bulb	33
Tetraoxygenated											
46			OH	OMe		-O-CH_2O-			3*R*, −12.3	*Sansevieria trifaciata* [A], aerial part	51
47		OH			OH	OH		OH	3*S*, +35	*Caesalpinia bonduc* [F], bark	52
48	OH		OH			OH	OMe		3*R*, +67.5	*Massonia bifolia* [A], bulb	53
49	OH		OMe			OH	OH		3*R*, −27	*Bellevalia flexuosa* [A], bulb	54
50	OH		OH			OH	OMe		3*S*, +5.2	*Rhodocodon campanulatus* [A], bulb	55
51	OH		OH		OH		OMe	3*R*	3*R*, −36.1	*P. odoratum* [A] rhizome	50
52	OH	OH	OH				OMe		3*R*, −36	*B. flexuosa* [A], bulb	54
53			OMe		OH	OH		OH	3*S*, +33	*B. flexuosa* [A], bulb	52
54	OMe	OH	OMe				OH		-	*Scilla nervosa* [A], bulb	56
55	OH	OMe	OMe		OH				+0.5	*P. oleracea* [Pt], aerial part	48
56	OH		OMe		OH		OMe		3*R*, −8.0	*P. sibircum* [A], rhizome	47
57	OMe		OH	OMe			OMe		3*R*, +41.5	*D. cochinchinensis* [A], resin	11

(Continued)

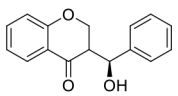
Table 2. Continued

No	Dioxygenated								Mp, *R/S*, $[\alpha]_D$	*Source* [Family][a], part of plant	References
	5	6	7	8	2′	3′	4′	5′			
58	OMe	OMe	OMe		OH				+0.3	*P. oleracea* [Pt], aerial part	[48]
59	OH	OMe	OMe				OMe		-	*S. nervosa* [A], bulb	[56]
60	OMe	OMe	OMe				OMe		3*S*, +9	*U. depressa* [A], whole plant	[46]
61	OH	Me	OH		OH		OH		3*R*, −15.3	*O. japonicus* [A], root	[24]
62	OH	Me	OMe		OH		OMe		3*R*, −25	*O. japonicus* [A], tuber	[22]
63	OMe	Me	OH			-O-CH_2O-			3*R*, +42.3	*O. japonicus* [A], root	[23]
64	OH	Me	OH			OH	OH		3*R*, −4.24	*Bessera elegans* [A], bulb	[57]
65	OH		OH	Me	OH		OH		+2.8	*Gan luo Xin*[d]	[58]
66	OH	Me	OMe		OH		OH		3*R*, −14.6	*L. platyphylla* [A], root	[49]
67	OH		OH	Me	OH		OH		3*R*, −24.7	*P. odoratum* [A], rhizome	[50]
68	OH		OH	Me	OH		OMe		3*R*, −8.2	*Polygonatum cyrtonema* [A], rhizome	[59]
69	OH	Me	OH	Me	OH		OH		−2.1	*Gan luo Xin*[d]	[58]
70	OMe	Me	OMe			OCH_2O			3*R*, +67.1	*O. japonicus* [A], root	[23]
71	OH	Me	OH	Me		OH	OMe		229°C to 230°C; ([e]) −44.9	*P. odoratum* [A], root	[60]
72	OH	Me	OH	Me	OH		OMe		168°C to 169°C, (±)	*P. odoratum* [A], root	[60]
73	OH	Me	OH		OH		OMe		3*R*, −16.4	*P. cyrtonema* [A], rhizome	[61]
74	OH	Me	OGlc	CHO		OCH_2O			−81.4	*O. japonicus* [A], root	[26]
75	OMe	Me	OGlc	CHO		OCH_2O			−127.7	*O. japonicus* [A], root	[26]
				Pentaoxygenated							
76	OH	OMe	OMe			OH	OH		3*S*, +17.4	*Scilla scilloides* [A], bulb	[62]
77	OH	OH	OMe	OMe			OH		3*R*, −14	*Bellevalia eigii* [A], bulb	[63]
78	OH	OH	OMe			OH	OMe		3*S*, +29.4	*R. campanulatus* [A] bulb	[55]
79	OH		OMe	OMe		OH	OH		3*R*, −86	*B. eigii* [A], bulb	[63]
80	OMe		OMe	OH		OH	OH		102°C to 104°C	*Scilla persica* [A], bulb	[64]
81	OH	Me	OH	OMe	OH		OMe		-	*O. japonicus* [A], rhizome	[27]
81b	OH	Me	OH	OMe	OH		OMe		−58.6	*P. odoratum* [A], rhizome	[65]
82	OH		OMe	OMe		OH	OMe		3*R*, −66	*B. eigii* [A], bulb	[63]
83	OMe	OMe	OMe			OCH_2O			3*S*, +12	*U. depressa* [A], whole plant	[46]
	Hexaoxygenated										
84	OH	Me	OH	OMe	OH	OH	OMe		3*R*, −14.4	*O. japonicus* [A], root	[26]

[a]A, Asparagaceae; Ar, Araliaceae; F, Fabaceae; Po, Polygonaceae; Pt, Portulacaceae.
[b]Substitutent at C-8 is a 2″-veratroyl-substituted-*C*-glucoside.
[c]*O*-[α-rhamnopyranosyl-(1→6)-β-glucopyranosyl.
[d]*Gan Luo Xin* is a traditional Chinese medicine for the treatment of hepatitis B formulated using 20 herbs including *Polygonatum sibiricum*.
[e]This compound was isolated as 84.9% 3*R* and 15.1%3*S*.



85-102



103-104

Table 3. Group B-2: 3-Hydroxy-3-Benzylchroman-4-Ones and 9-Hydroxy-3-Benzylchroman-4-Ones: Compounds **85 to 102**; and Compounds **103 to 104**.

	Tri-oxygenated								Mp (°C), 3 R/S $[\alpha]_D$	*Source* [Family][a], part of plant; $3\alpha/\beta$	References
	5	6	7	8	2′	3′	4′	5′			
85			OH			OMe	OH		183°C; 3*S*, +49.2	*C. sappan* [F], heartwood, β	66
86	OH		OMe				OH		3*S*, −63	*B. eigii* [A], bulb, α	63
87			OH	OMe			OH		3*R*,	*D. cochinchinensis* [A], leaves	65
88	OH		OH				OMe		3*S*, −85	*D. cochinchinensis* [A], α	11
89	OH		OMe				OMe		3*S*, −96	*B. flexuosa* [A], bulb, α	54
90	OH	Me	OH				OMe		3*R*, −24.0	*Dracaena cambodiana* [A], stem, β	67
91	OH	Me	OMe				OH		81°C to 83°C; 3*R*, +178.7	*Smilax glabra* [S], rhizome, β	68
				Tetraoxygenated							
92	OH		OH			OH	OMe		−76.92	*Pseudoprospero firmifolium* [A], bulb	69
93	OH		OMe	OMe			OH		−170	*B. flexuosa* [A], bulb, α	54
94	OMe	OMe	OMe				OH		+18	*U. depressa* [A], whole plant, β	46
95	OH		OMe			OMe	OMe		3*S*, −86.11	*P. firmifolium* [A], bulb	69
96			OH	OMe		OCH_2O			3*S*, −28.3	*Sansevieria trifasciata* [A], aerial β	51
97	OMe	OMe	OMe				OMe		3*S*, +26	*U. depressa* [A], whole plant, β	46
98	OH	Me	OH	Me		OCH_2O			3*R*, −97.6	*Ophiopogon japonicas* [A], root, β	28
99	OH		OMe	OMe		OMe		OMe	−131.6	*P. firmifolium* [A],	69
100	OH		OMe	OMe		OH	OMe		−75.0	*P. firmifolium* [A], bulb	69
101	OH	OH	OMe			OH	OMe		−38.46	*P. firmifolium* [A], bulb	69
102	OMe	OMe	OMe			OCH_2O			3*R*, +23	*U. depressa* [A], whole plant, β	46
103	OH	OMe	OH				OH		240°C to 242°C	*Lespedeza juncea* [F], aerial	70
104	OH	OMe	OH	Me			OH		190°C to 192°C	*L. juncea* [F], aerial	70

[a]A, Asparagaceae; F, Fabaceae; R, Rosaceae; S, Smilacaceae.

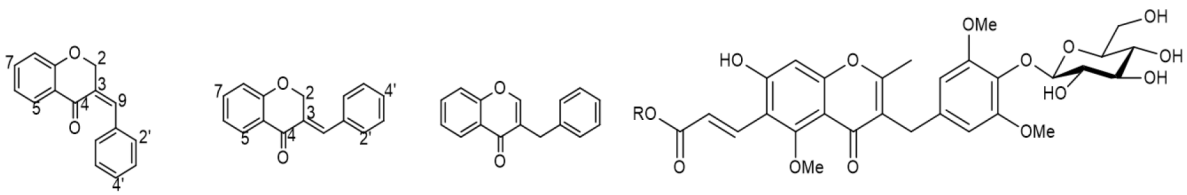
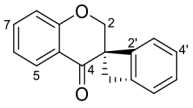


Table 4. Group C: $\Delta^{3,9}$-*Z* (**105-106**), *E* (**107-127**), and $\Delta^{2,3}$-Unsaturated (**133-135**) -3-Benzylchroman-4-Ones.

105			OH	OH			OMe		-	*Caesalpinia diigyna* [F], root	[71]
106			OH	OMe			OMe		-	*Caesalpinia millettii* [F], stem	[72]
107			OMe				OMe		130°C to 132°C	*Caesalpinia pulcherima* [F], whole	[73]
108	OH		OMe		OH				146°C	*P. oleracea* [Po], aerial	[48]
109			OH			$O\text{-}CH_2O$			-	*C. pulcherima* [F], aerial	[74]
110			OMe			$O\text{-}CH_2O$			-	*C. pulcherima* [F], aerial	[74]
111			OH			OH	OMe		-	*C. pulcherima* [F], aerial	[74]
112			OMe			OMe	OMe		-	*C. pulcherima* [F], aerial	[74]
113	OH		OGlc				OH		−67.4	*P. odoratum* [A], root	[60]
114	OH	Me	OH	Me			OH		217°C to 218°C	*P. odoratum* [A], root	[60]
115	OH		OH			OH	OH		-	*Ledebouria ovatifolia* [A], bulb	[75]
116	OH		OMe			OH	OH		-	*Massonia biolia* [A], bulb	[53]
117	OH		OMe	OMe			OH		-	*B. eigii* [A], bulb	[63]
118			OH			OMe	OMe	OMe	202°C to 204°C	*C. pulcherima* [F], whole	[73]
119		OMe	OMe			OH	OMe		168°C to 170°C	*C. pulcherima* [F], aerial	[74]
120	OH	Me	OH	Me		OH	OH		233°C to 234°C	*P. odoratum* [A], rhizome	[76]
121	OH	OH	OH	Me			OH		-	*Eucomis pallidiflora* subsp *pole-evansii* [A], bulb	[77]
122			OH		OH	OH	OH	OH	-	*C. sappan* [F], heartwood	[30]
123	OH		OMe	OMe		OH	OH		-	*B. eigii* [A], bulb	[63]
124	OH	OH	OH			OH	OMe		-	*R. campanulatus* [A], bulb	[55]
125	OH	Me	OH				OH		-	*A. asphodeloides* [A], rhizome	[41]
126	OMe	Me	OMe	OH		OH	OH		-	*S. persica* [A], bulb	[78]
127	OH	Me	OH	OMe		OH	OH		250°C to 251°C	*P. odoratum* [A], rhizome	[73]
128	OH	CHO	OH	Me			OMe		-	*O. japonicus* [A], root	[25]
129	OMe	Me	OH	CHO			OMe		-	*O. japonicas* [A], root	[25]
130	OH	Me	OH		OH		OH		-	*O. japonicus* [A], root	[24]
131	OH	Me	OH	OMe	OH		OH		-	*O. japonicus* [A], root	[28]
132			OH		OH	OH	OH	OH	-	*C. sappan* [F], heartwood	[30]
133	See structure R = H								+14.5	*P. domestica* [R] shoot	[35]
134	See Structure R = Propyl								+16.0	*P. domestica* [R] shoot	[35]
135	See structure R = *p*-hydroxyphenyl								+24.0	*P. domestica* [R] shoot	[35]

[a]A, Asparagaceae; F, Fabaceae; Po, Polygonaceae; R, Rosaceae.

values of 0.2 and 0.7 against [H1N1], 0.3 and 1.1 against [H3N2], and 0.4 and 1.0 for [H9N2]. These 2 were in a class of their own and were singled out as lead compounds with high potency against 3 viral NAs. The study also suggested that the α, β-unsaturated group of sappanone A (**159**) (Figure 7) was critical for activity as the others without this functional group showed higher IC_{50} values in the range 63 to 204 μM. A further observation was also that the 4*R* HIF 4-*O*-methylepisappanol was more active with IC_{50} values of 63.2 μM [H1N1, H3N2] and 42.8 μM for [H9N2] than the *4S* isomers 4-*O*-methylsappanol (**8**) with IC_{50}s of 94.5 μM [H1N1], 134.7 [H3N2], and 99.6 μM for [H9N2]. Similar values were obtained for sappanol and episappanol.[29] Cruz et al[84] tested various compounds, including brazilin (**3**) and hematoxylin (**161**), isolated from the methanolic extract of *Haematoxylon brasiletto* against 12 bacteria and the fungus *Candida albicans*, but found these 2 compounds only weakly active against the tested organisms.



136-141

Table 5. Group D: Scillascillins: Compounds **136 to 141**.

No	5	6	7	8	2′	3′	4′	5′	Mp; $[\alpha]_D$	*Source* [Family],[a] part of plant	References
136	OH	Me	OH			OH	OMe		+6.96	*B. elegans* [A], bulb	57
137	OH		OH			OH	OMe	OMe	+65.6	*S. scilloides* [A], bulb	62
138	OH		OMe			OH	OMe	OH	+32	*Drmiopsis barteri* [A], bulb	79
139	OH		OMe			OH	OMe	OMe	+40	*Ledebouria socialis* [A] bulb	75
140	OH		OH			OMe	OMe	OMe	197°C to 199°C;	*D. barteri* [A], bulb	79
141	OH		OMe			OMe	OMe	OMe	+55.0	*D. barteri* [A], bulb	79

[a]A = Asparagaceae.

Antihyperglycemic Properties

The hypoglycemic properties of HIFs have been assessed in terms of their ability to modulate the insulin receptor, lower blood glucose, and regulate the levels of various kinases (protein kinase C, phosphotidylinositol 3-kinase, pyruvate kinase, and 6-phosphofructo-2 kinase), which are involved in the gluconeogenesis and glycolytic pathways and glucose transport.[60]

The 2 protein components of the glucose absorption system of the intestine are the sodium-dependent glucose transporter-1 (SGLT1), and glucose transporter (GLUT). Several HIFs have been evaluated for their ability to either activate adenosine monophosphate-activated protein kinase (AMPK) or to inhibit the activity of the GLUT transmembrane carriers.[85,86] Adenosine monophosphate protein kinase activators are potential therapeutic candidates for the treatment of diabetes as they can increase the uptake of glucose via membrane translocation of GLUT 4. Six previously known HIFs from the rhizomes of *P. odoratum* were evaluated for their ability to activate AMPK, and 3 of them (**153**, **154,** and **157**) exhibited significant activation effects. **153**, **154,** and **157** (Figure 8) also emerged as the most effective of 19 other HIFs as novel potent GLUT2 inhibitors. In addition, they also demonstrated synergistic inhibition of glucose transport when combined with previously identified SGLT1 specific antagonists.[85]

In another earlier study[87] 2 of the HIFs, **155** and **157**, were identified as the active constituents of *P. odoratum* acting as peroxisome proliferator-activator receptor agonists (PPARAs) by binding to PPARc ligand-binding pocket. The authors caution the herbal use of the plant against side effects resulting from PPARC activation.

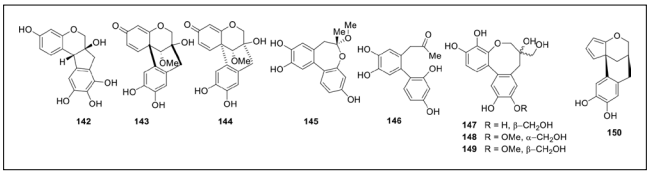


Figure 6. Group E: Rearranged HIFs: Compounds **142 to 150**.

The 3 esters, prunuside A to C, with a rather unusual substitution and carbon framework, were obtained from the shoots of the Rosaceae plant, *P. domestica.* The source of these prunusides is a tree whose fruits are edible and used to lower blood sugar in India and Pakistan. The HIFs (**133-134**) were assayed for α-glucosidase inhibitory activity.[35] It is known that α-glucosidase inhibitors, such as acarbose, miglitol, and voglibose, can reduce the rate of cleavage of glucose from dietary carbohydrates and hence suppress postprandial hyperglycemia. Accordingly, Kosar et al[35] assessed the α-glucosidase inhibitory activity of **133 to 134** and found the IC_{50} ± SEM (μM) to be: 216.6 ± 0.027, 268.4 ± 0.047, and 203.6 ± 1.700, respectively. The value obtained for the

Table 6. Antioxidant Data of HIFs Using DPPH Radical Scavenging (System A), and B-Carotene/Linoleic Acid (System B) Assay Systems.

HIF	System A IC_{50} (μg/mL)	System B	References
2	3.11	57.0	33
3	8.8	-	82
6	14.5	-	82
38	112	-	36
40	23.2	-	36
41	28.7	-	36
44	212.4	26.0	36
45	273.1	11.4	36
151	84.3	41.9	36
152	39.4	64.5	36
154	80.2	42.0	36
BHT	103		33
BHA	98.7		33

positive control, deoxynojirimycin, used in the study was 281.3 ± 2.8. All the esters were more active than the control, particularly **134**, which is probably due to the pharmacophoric contribution of the hydroquinone moiety.

Adenosine monophosphate protein kinase activation is known to affect glucose and lipid metabolism, gene expression, and protein synthesis. Two out of 6 HIFs isolated from the rhizomes of *P. odoratum*, (3*R*)-5,7-dihydroxyl-6-methyl-8-methoxyl-3-(4′-hydroxybenzyl)-chroman-4-one and (3*R*)-5,7-dihydroxyl-6,8-dimethyl-3-(4′-hydroxybenzyl)-chroman-4-one were found to have significant activation effects.[86]

Cytotoxic Activities

The cytotoxicity of HIFs on various cell lines, including tumor cells has been documented.

Uesawa et al[88] undertook a SUGITA3 quantitative structure-activity relationships of 16 HIFs (3-benzylidinechromanones) and concluded that those 3-benzylidenechromanone derivatives that have a methoxy group at position C-7 of the chromanone ring and either hydroxyl or methoxy group at C-4′ of the B ring showed relatively higher tumor-specificity values, exceeding those of doxorubicin and 5-fluorouracil. The paper concluded by pointing out that molecular shape, size and polarization are useful indicators for the evaluation of tumor specificity of this class of compounds. Compound **132** (caesalpiniaphenol G) isolated from the heartwood of Vietnamese *C. sappan* contains a hydroxyl group at C-7 and 4 such groups in ring B.[30] It was isolated together with the highly modified caesalpiniaphenol and structurally rearranged compound caesalpiniaphenol H (**148**). Both compounds showed potent inhibitory activity against HL-60 cancer cell lines with respective IC_{50} values of 16.7 and 22.5 µg/mL. Treating HL-60 cells with **132** resulted in inhibition of growth and introduction of apoptosis.

The anticancer potential of intricatinol (**160**) (Figure 9) in combination with the known anticancer drug cisplatin in nonsmall-cell lung carcinoma (A549 cells) was demonstrated by the observed apoptosis showing DNA fragmentation and Annexin V positive cells. It was shown that treatment with the HIFs alone reduced the viability of the A549 cells in a dose-dependent manner, as reported by Singh et al[89]

In studying the roles of protein tyrosine kinase (PTK) inhibitors for cancer chemoprevention, Lin et al[90,91,108] found that hematoxylin (**161**) was a "most remarkable" c-Src inhibitor in an orthogonal compound-mixing library of 32 200 compounds, and that the inhibition was associated with PTK

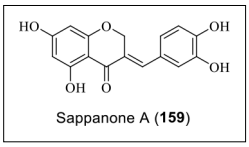


Figure 7. Example of antiviral HIF.

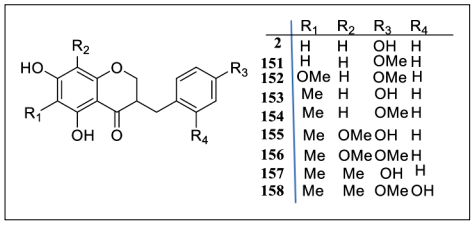


Figure 8. Examples of antihyperglycemic HIFs.

phosphorylation and subsequent downstream signaling pathways. Subsequently,[92] brazilein, an oxidized form of hematoxylin, was found to inhibit adipocyte differentiation, inducing apoptosis through capsase-3 activity.

In a recent study Yang et al[93] investigated the antitumor properties of protosappanin B (**134**). Both in vitro, by trypan blue exclusion and MTT assays, and in vivo, on H22 mouse liver cancer cells invasion and the survival of tumor-bearing mice were investigated. In both cases, they found that protosappanin B (**134**) exerts marked antitumor effects.

Antiproliferative activity guided investigation of the South African plant *U. depressa* led to the isolation of 6 new HIFs **33**, **60**, **83**, **94**, **97**, **102** and all except **33** were shown to possess good antiproliferative activity against the A2780 ovarian cancer, A2058 melanoma, and H522-T1 human nonsmall-cell lung cancer cells, and urgineanin A (**97**) had submicromolar activity against all 3 cell lines.[46]

The finding that 5,7-dihydroxy-3-(4′-hydroxy-3′-methoxybenzyl)-6-methoxyhomoisoflavanone (cremastrone) possesses antiangiogenic activity both in vitro and in vivo and was a potent inhibitor of the proliferation of human umbilical vein endothelial cells,[94] prompted further work to identify other natural HIFs and their derivatives which may be developed as small molecule therapeutic agents.[95,96] Among natural HIFs methylophiopogonanone A (**9**) and B have been identified as potentially significant hits. The former (**9**) has been shown to protect against cerebral ischemia/reperfusion injury and attenuates blood-brain barrier disruption in vitro.[97]

Synthesis of Naturally Occurring HIFs

The commonly employed methodologies for the construction of the homoisoflavonoid scaffolds can be categorized into 2 general groups:

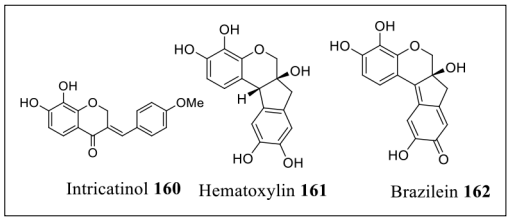
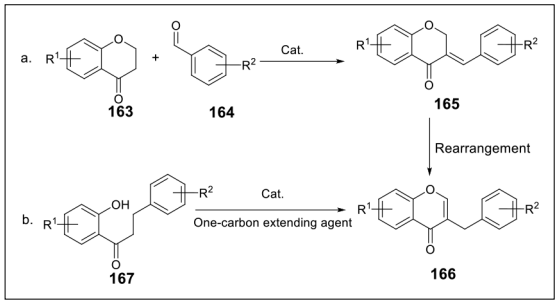


Figure 9. Cytotoxic HIFs.

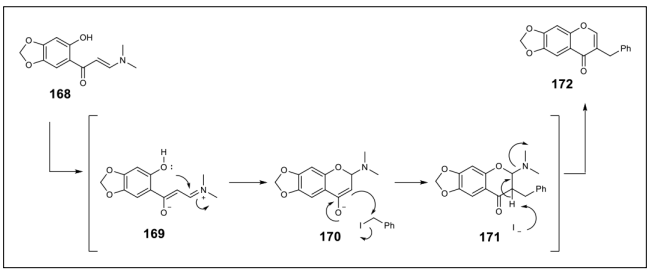


Scheme 1. General protocols for the synthesis of HIFs.

1. Aldol condensation of pre-prepared chroman-4-ones with aryl aldehydes (Scheme 1a) provides HIFs (**165**) with an *exo*$\Delta^{3,9}$ double bond. Furthermore, the homoisoflavonoid isomer **166** with the *endo*$\Delta^{2,3}$ double bond can be prepared via migration of the *exo* double bond by treatment with a base or rhodium catalysts;
2. Acid catalyzed cyclization of dihydrochalcones **167,** in the presence of one-carbon extension reagents, such as CH_3SO_2Cl//DMF, HCO_2Et/Na, 2,4,6-trichloro-1,3,5-triazine/DMF, and $HC(OEt)_3/HClO_4$, yields HIFs **166** with the *endo*$\Delta^{2,3}$ double bond (Scheme 1b).

Since our last review, few novel synthetic methodologies have been developed for the construction of the homoisoflavone scaffolds. The cyclobenzylation reaction of (*E*)-3-(dimethylamino)-1-(2-hydroxy-4,5-methylenedioxyphenyl)prop-2-en-1-one **168** and benzyl bromide at 80°C in the presence of NaI is a recent methodology for the synthesis of homoisoflavonoid derivatives **172** (Scheme 2).[98] The reaction is proposed to proceed as shown in Scheme 2 and involves intramolecular cyclization followed by benzylation of the resulting enolate **170** and subsequent elimination of the dimethyl amine group to provide the homoisoflavonoid **172**.

In a serendipitous discovery, Lee and co-workers developed an interesting ruthenium-catalyzed synthesis of 2-arylhomo-isoflavonoid **179** scaffolds by reacting salicylaldehyde and alkynoic acids via C-H activation, as depicted in Scheme 6.[99] The reaction is proposed to proceed via initial formation



Scheme 2. BnBr, NaI, acetone, 80°C, 5 hours, 80%.

of chalcone **175** that undergoes intramolecular cyclization to provide the flavonoid intermediate **176**.

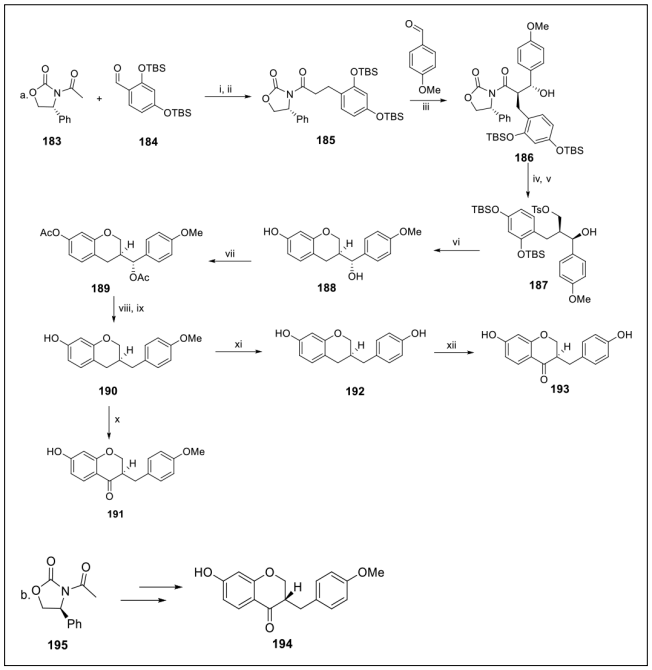
Aldol condensation between the flavonoid **176** and an additional salicylaldehyde provides homoisoflavonoid **178** with an *exo*$\Delta^{3,9}$ double bond that rearranges to the *endo*$\Delta^{2,3}$ isomer **179**. However, the rearrangement reaction from the *exo*$\Delta^{3,9}$ double bond to the *endo*$\Delta^{2,3}$ double bond was uncontrollable to prepare selectively either the homoisoflavonoid **178** or **179** as desired. Bhagavathy and co-workers reported an interesting tandem thermal [1,3]-[1,3]-*para* and [1,3]-*ortho*- rearrangement of chromone-3-ylmethyl aryl ethers for the synthesis of homoisoflavonoids **181** and **182** as shown in Scheme 7.[100] Despite its simplicity and generality, the protocol has not been applied to the synthesis of natural homoisoflavonoids.

The major advance made in the synthesis of HIFs post 2007 is the focus on asymmetric synthesis. Yu et al, for instance, reported the asymmetric synthesis of several sappanin-type natural HIFs (**190** to **194**)[101] using Evans' chiral auxiliaries **183** and **195.**[102] The use of Evans' chiral auxiliary **183** led to the synthesis of homoisoflavan **190** in >99% ee *via* aldol, intramolecular cyclization and deoxygenation reactions as key steps, as shown in Scheme 3. By analogy, using Evans' chiral auxiliary **195**, the synthesis of enantiomer **194** was achieved in >099% ee (Scheme 3). Oxidation of **190** using DDQ gave **191**, while demethylation of **190** afforded **192** and upon treatment with DDQ provided homoisoflavanone **193** (Scheme 3) (**192** and **193** have been reported from commercial Dragon's blood *Dracaena draco* and *D. cambodiana.*[103])

By exploiting the versatility of Sharpless dihydroxylation and epoxidation reactions, a number of sappanone-type natural HIFs have been prepared. This is demonstrated by Kim and co-workers who successfully synthesized (+)-urgineanin A-D and (−)-urgineanin A (**196a-d**) (**196a-d** were isolated from the South African plant *U. depressa.*[46]), as depicted in Scheme 8.[104] Palladium-catalyzed allylic arylation of **197** with arylboronic acids provided coupled product **198**. Asymmetric dihydroxylation using $(DHQ)_2PHAL$, followed by a regioselective oxidation led to the preparation of (+)-urgineanin A-D (**196a-c**) while the use of $(DHQD)_2PHAL$ as a dihydroxylating agent afforded (−)-urgineanin A (**196d**).

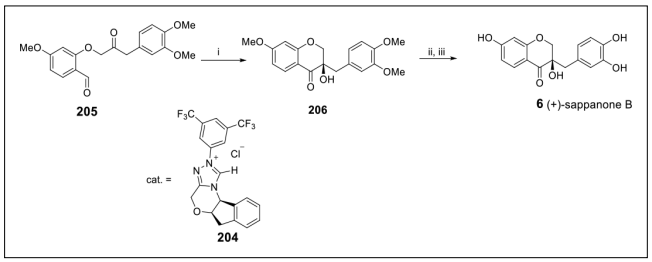
Similarly, by changing the substituents at the phosphorus atom of enol phosphates **201**, synthesis of enantiopure (*R*)-(+)-eucomol **202** and (*S*)-(−)-eucomol **203** (**202/203** was first isolated from the bulbs of *Eucomis bicolor* Bak.[105]**)** was achieved via asymmetric dihydroxylation as shown in Scheme 9.[103]

In addition to asymmetric dihydroxylation strategies for the synthesis of enantiopure sappanones, an enantioselective cyclization protocol has also been reported. Takikawa and Suzuki designed and synthesized a modified Rovis catalyst **204**, a chiral triazolium salt that possesses a strongly electron-withdrawing group and applied it in the enantioselective benzoin cyclization of suitably prepared keto-aldehydes

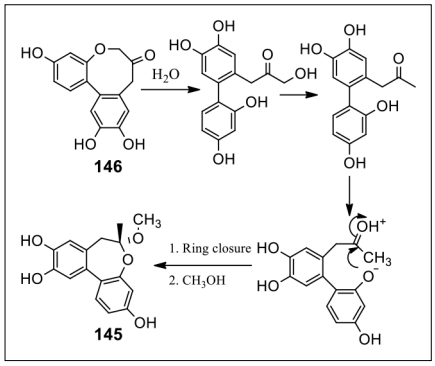


Scheme 3. (i) $TiCl_4$, (+)-sparteine, DCM, 0°C, 2 hours, 83%; (ii) Pd/C, EtOAc, rt, 5 hours, 95%; (iii) $TiCl_4$,TMEDA, DCM, −20°C, 2 hours, 62%; (iv) $NaBH_4$,THF/H_2O, 5 hours, 86%; (v) *p*-TsCl, *n*-Bu_2SnO, DMAP, Et_3N, MeCN, rt, 3 hours, 84%; (vi) *n*-Bu_4NF,THF, rt, 30 minutes, 92%; (vii) Ac_2O, Et_3N, DMAP, DCM, rt, 30 minutes, 94%; (viii) Et_3SiH, CF_3CO_2H, DCM, 0°C, 30 minutes, 88%; (ix) K_2CO_3, MeOH, rt, 30 minutes, 92%; (x) 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), dioxane, H_2O, rt, 30 minutes, 74%; (xi) BBr_3, CH_2Cl_2, rt, 1 hour, 89%; (xii) DDQ, dioxane, H_2O, rt, 30 minutes, 57%.

205 for the preparation of (+)-sappanone B **6** (Scheme 4).[107] The presence of the strongly electron-withdrawing substituent (–CF_3) on the aromatic ring of the triazolium salt suppresses enolization that leads to formation of side products via aldol reactions. This is due to the ease with which the hydrogen can be abstracted to generate a carbene catalyst by the weaker base, Et_3N, which is not capable of enolizing the substrate. Furthermore, the generated carbene is less basic to enolize the keto-aldehyde **205**.



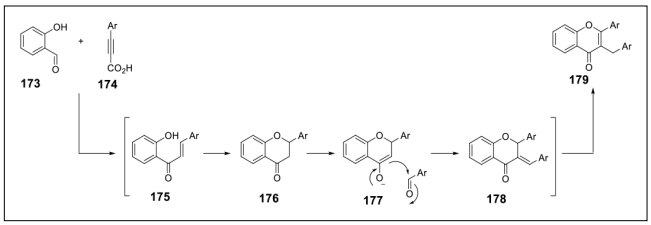
Scheme 4. (i) cat. (15 mol %), Et_3N, toluene, rt, 12 hours, 92%, 95% ee; (ii) $NaSC_{12}H_{25}$, DMF, 80°C, 5 hours, 92%; (iii) BBr_3, DCM, 0°C, 0.5 hour, 85%.



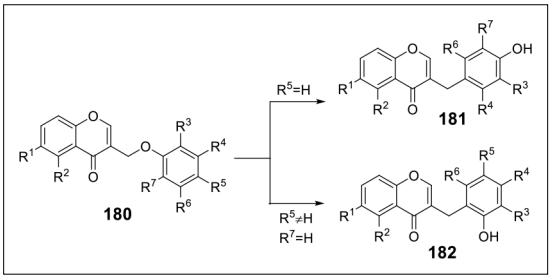
Scheme 5. Biogenetic scheme to caesappin A (**145**).

The epoxidation and dihydroxylation reactions have been also instrumental in the total synthesis of (±)-brazilein, (±)-brazilin, and (±)-brazilane.[108,109] Zhang and co-workers utilized asymmetric Sharpless dihydroxylation reaction for the enantioselective synthesis of (+)-brazilin (**3**), (−)-brazilein (**162**), and (+)-brazilide A (**214**) from a common starting material, as shown in Scheme 10.[110] Accordingly, coupling of indene **207** and phenol **208**, followed by asymmetric dihydroxylation led to the formation of diol **210** in 81% ee. Acid catalyzed intramolecular cyclization and deprotection of the benzoate protecting group afforded the key intermediate tetracyclic **211**. Demethylation of **211** provided (+)-brazilin (**3**). DIB-mediated oxidation of (+)-brazilin (**3**) gave (−)-brazilein (**162**). Further manipulation of **211** provided **212** that underwent diastereoselective epoxidation to form epoxide **213**. Lactonization of epoxide **213** afforded (+)-brazilide A (**214**) in 82% yield.

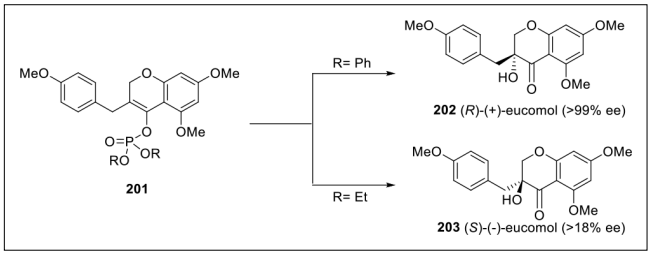
In conclusion, HIFs are now recognized as an important subclass of flavonoids. They display broad structural diversity and biological properties. They occur principally in 2 plant families, Asparagaceae and Fabaceae, and several genera including *Ophiopogon, Caesalpinia*, *Polygonatum*, *Ledebouria*, *Belevalia*, *Dracaena*, *Hematoxylon*, *Liriope*, *Portulaca*, *Scilla*, *Pseudoprospera,* and *Urginea*. Many species belonging to these genera are important ingredients in many Chinese, Indian, Japanese, and other countries' traditional medicine. HIFs are the major bioactive constituents of the popular medicinal plants *O. japonicus*,[7] *C. sappan*,[6] and of Dragon's blood (*Dracanea cinnabari*).[8] *Ophiopogon*



Scheme 6. [Ru(*p*-cymene)Cl_2]$_2$ (2.5 mol %), CsOAc, DMSO, 120°C, 12 hours, 64% to 82%.

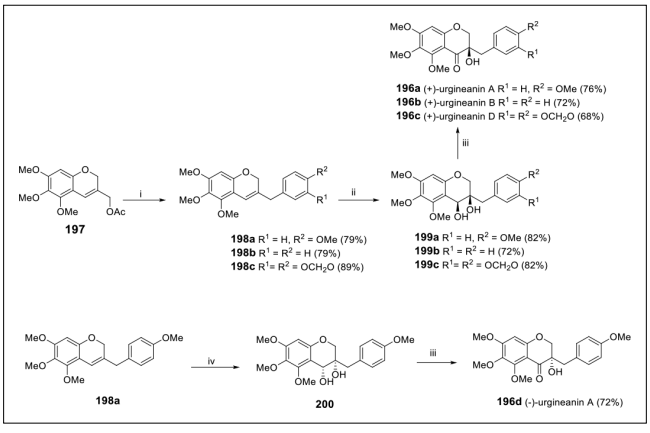


Scheme 7. Ph_2O, Cs_2CO_3, reflux, 65% to 84%.



Scheme 9. $(DHQD)_2PHAL$, OsO_4, $CH_3SO_2NH_2$, $K_3Fe(CN)_6$, K_2CO_3, $^tBuOH/H_2O$, 0°C.

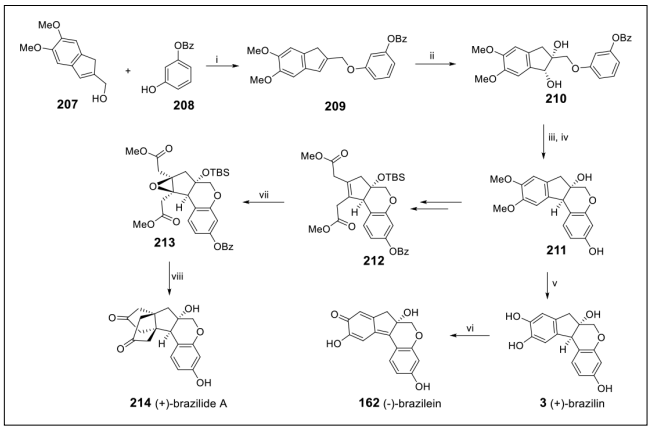
japonicus alone has yielded more than 38 HIFs,[7] more than any other species, followed by *Caesalpinia*, *Polygonatum*, and *Ledebouria* species. Homoisoflavonoids have been shown to possess a wide range of pharmacological properties including antimicrobial, antimutagenic, antioxidant, immunomodulatory, cytotoxic, antiangiogenic, anti-inflammatory, antiphotoaging, hypoglycemic, vasorelaxant, hepatoprotective, and antiacne activities. Brazilin (**3**) is the major and most biologically active of the 4 HIFs found in the heartwood of *C. sappan*.[6] The folkloric uses of brazilin include antioxidant, antibacterial, anti-inflammatory, antiphotoaging, hypoglycemic, vasorelaxant, hepatoprotective, and antiacne applications. The scientific evidence generated for brazilin strongly suggests its potential to be developed as a medicinal compound with application in the food, beverage, cosmetics, and pharmaceutical industries. Brazilin may also have applications as a preservative and coloring agent in the food processing industries. Some of the significant pharmacological data generated during the current review period include those of brazilin (**3**), sappanone B (**6**),[80] ledebourin B (**40**), and ledebourin C (**41**)[36] as antioxidants; sappanone A (**159**),[83] ophiopogoside A (**62**), ophiopogoside B (**63**), and ophiopogonanone G (**69**)[26] for their anti-inflammatory properties, and brazilin (**3**) and sappanone A (**159**) for their exceptional antiviral potencies[29]; HIFs **155** and **157**,[87] and **133 to 134**[35] for their potential application as hypoglycemic agents; and methylophiopogonanone A (**9**),[86] urgineanin A (**97**),[46] protosappanin B (**134**),[93] intricatinol (**160**),[89] and hematoxylin (**161**)[90] for their cytotoxic and tumor-inhibiting applications. The increasing importance of HIFs has also raised the interest of synthetic organic and medicinal chemists. Both the earlier[3] and the current reviews include various synthetic methodologies for the total synthesis of natural HIFs, as well as their derivatives. The development of asymmetric synthesis, transition metal catalyzed coupling reactions as well as H-activation synthetic methodologies is less explored for the synthesis of HIF.



Scheme 8. (i) $ArB(OH)_2$, $Pd(PPh_3)_4$, K_3PO_4, THF, 150°C; (ii) OsO_4, $(DHQ)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$, 0°C; (iii) IBX; (iv) OsO_4, $(DHQD)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$, 0°C.

Acknowledgments

This paper was written during B.M.A.'s 1-month stay (September 2018) at the Stellenbosch Institute for Advanced Study (STIAS). B.M.A. is grateful to the leaders of this enabling institution and the staff who have been very gracious and helpful. Research Centre for Synthesis and Catalysis of the Department of Chemistry at UJ and the National Research Foundation (NRF)-DST are also acknowledged for financial support.



Scheme 10. (i) DEAD, Ph_3P, THF, −78°C, 60%; (ii) AD-mix-b, OsO_4, $MeSO_2NH_2$, *t*-BuOH/H_2O/DCM, 3 days, 85%, 81% ee; (iii) PPTS, toluene, 90°C, 80%; (iv) LiOH, THF/MeOH, 67%, 99.8% ee; (v) BBr_3, DCM, 81%; (vi) $PhI(OAc)_2$, THF, 0°C, 76%; (vii) *m*-CPBA, 32°C, 3 days, DCM, 22%; (viii) a. $BF_3{\cdot}Et_2O$, DCM; b. 65% H_2SO_4, AcOH, 110°C, 82%.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This article was financially supported by the Research Centre for Synthesis and Catalysis of the Department of Chemistry at UJ and the National Research Foundation (NRF)-DST.

References

1. Dewick PM. Biosynthesis of the 3-benzylchroman-4-one eucomin. *J Chem Soc Chem Commun*. 1973;13(13):438-439.
2. Dewick PM. Biosynthesis of the 3-benzylchroman-4-one eucomin in *Eucomis bicolor*. *Phytochemistry*. 1975;14(4):983-988.
3. Abegaz BM, Mutanyatta-Comar J, Nindi M. Naturally occurring homoisoflavonoids: phytochemistry, biological activities and synthesis. *Nat Prod Commun*. 2007;2(4):475-498.
4. Du Toit K, Drewes SE, Bodenstein J. The chemical structures, plant origins, ethnobotany and biological activities of homoisoflavanones. *Nat Prod Res*. 2010;24(5):457-490.
5. Lin L-G, Liu Q-Y, Ye Y. Naturally occurring homoisoflavonoids and their pharmacological activities. *Planta Med*. 2014;80(13):1053-1066.
6. Nirmal NP, Rajput MS, Prasad R, Ahmad M. Brazilin from *Caesalpinia sappan* heartwood and its pharmacological activities: a review. *Asian Pac J Trop Med*. 2015;8(6):421-430.
7. Chen M-H, Chen X-J, Wang M, Lin L-G, Wang Y-T. *Ophiopogon japonicus*—a phytochemical, ethnomedicinal and pharmacological review. *J Ethnopharmacol*. 2016;181:193-213.
8. Gupta D, Bleakley B, Gupta RK. Dragon's blood: botany, chemistry and therapeutic uses. *J Ethnopharmacol*. 2008;115(3):361-380.
9. Zhu Y, Zhang P, Yu H, Li J, Wang M-W, Zhao W. Anti-*Helicobacter pylori* and thrombin inhibitory components from Chinese Dragon's blood, *Dracaena cochinchinensis*. *J Nat Prod*. 2007;70(10):1570-1577.
10. Hu L, Wang F-F, Wang X-H, Yang Q-S, Xiong Y, Liu W-X. Phytoconstituents from the leaves of *Dracaena cochinchinensis* (Lour.) S. C. Chen. *Biochem Syst Ecol*. 2015;63:1-5.
11. Xu X, Cheng K, Cheng W, Zhou T, Jiang M, Xu J. Isolation and characterization of homoisoflavonoids from *Dracaena cochinchinensis* and their osteogenic activities in mouse mesenchymal stem cells. *J Pharm Biomed Anal*. 2016;129:466-472.
12. Xu P, Guan S, Feng R, Tang R, Guo D. Separation of four homoisoflavonoids from *Caesalpinia sappan* by high-speed counter-current chromatography. *Phytochem Anal*. 2012;23(3):228-231.
13. Ma C, Li G, Zhang J, Zheng Q, Fan X, Wang Z. An efficient combination of supercritical fluid extraction and high-speed counter-current chromatography to extract and purify homoisoflavonoids from *Ophiopogon japonicus* (Thunb.) Ker-Gawler. *J Sep Sci*. 2009;32(11):1949-1956.
14. Uddin GM, Kim CY, Chung D, Kim K-A, Jung SH. One-step isolation of sappanol and brazilin from *Caesalpinia sappan* and their effects on oxidative stress-induced retinal death. *BMB Rep*. 2015;48(5):289-294.
15. Sievänen E, Toušek J, Lunerová K, et al. Structural studies of homoisoflavonoids: NMR spectroscopy, X-ray diffraction, and theoretical calculations. *J Mol Struct*. 2010;979(1-3):172-179.
16. Hu X-R, Chou G-X, Zhang C-G. Flavonoids, alkaloids from the seeds of *Crotalaria pallida* and their cytotoxicity and anti-inflammatory activities. *Phytochemistry*. 2017;143:64-71.
17. Pescitelli G, Bruhn T. Good computational practice in the assignment of absolute configurations by TDDFT calculations of ECD spectra. *Chirality*. 2016;28(6):466-474.
18. Batista JM, Wang B, Castelli MV, Blanch EW, López SN. Absolute configuration assignment of an unusual homoisoflavanone from *Polygonum ferrugineum* using a combination of chiroptical methods. *Tetrahedron Lett*. 2015;56(44):6142-6144.
19. López SN, Sierra MG, Gattuso SJ, Furlán RL, Zacchino SA. An unusual homoisoflavanone and a structurally-related dihydrochalcone from *Polygonum ferrugineum* (Polygonaceae). *Phytochemistry*. 2006;67(19):2152-2158.
20. Midiwo JO, Omoto FM, Yenesew A, Akala HM, Wangui J, Liyala P. The first 9-hydroxyhomoisoflavanone, and antiplasmodial chalcones, from the aerial exudates of *Polygonum senegalense*. *Arkivoc*. 2007;ix:21-27.
21. Dzoyem JP, Kuete AHL, Kuete V, et al. Cytotoxicity and antimicrobial activity of the methanol extract and compounds from *Polygonum limbatum*. *Planta Med*. 2012;78(8):787-792.
22. Dang NH, Chung ND, Tuan HM, Hiep NT, Dat NT. Cytotoxic homoisoflavonoids from *Ophiopogon japonicus* tubers. *Chem Pharm Bull*. 2017;65(2):204-207.
23. Wang Y, Xu J, Zhang L, Qu H. Three new homoisoflavanones from *Ophiopogon japonicus* Ker-Gawler (Liliaceae). *Helv Chim Acta*. 2010;93(5):980-984.
24. Duan C-L, Kang Z-Y, Lin C-R, Jiang Y, Liu J-X, Tu P-F. Two new homoisoflavonoids from the fibrous roots of *Ophiopogon japonicus* (Thunb.) Ker-Gawl. *J Asian Nat Prod Res*. 2009;11(10):876-879.
25. Zhou C-X, Zou L, Mo J-X, et al. Homoisoflavonoids from *Ophiopogon japonicus*. *Helv Chim Acta*. 2013;96(7):1397-1405.

26. Hung TM, Thu CV, Dat NT, et al. Homoisoflavonoid derivatives from the roots of *Ophiopogon japonicus* and their in vitro anti-inflammation activity. *Bioorg Med Chem Lett*. 2010;20(8):2412-2416.
27. Zhao J-W, Chen D-S, Deng C-S, Wang Q, Zhu W, Lin L. Evaluation of anti-inflammatory activity of compounds isolated from the rhizome of *Ophiopogon japonicus*. *BMC Complement Altern Med*. 2017;17(1):1-12.
28. Li N, Zhang J-Y, Zeng K-W, Zhang L, Che Y-Y, Tu P-F. Anti-inflammatory homoisoflavonoids from the tuberous roots of *Ophiopogon japonicus*. *Fitoterapia*. 2012;83(6):1042-1045.
29. Min BS, Cuong TD, Hung TM, Min BK, Shin BS, Woo MH. Compounds from the heartwood of *Caesalpinia sappan* and their anti-inflammatory activity. *Bioorg Med Chem Lett*. 2012;22(24):7436-7439.
30. Hung TM, Hai NX, Nhan NT, et al. Cytotoxic activity of new phenolic compounds from Vietnamese *Caesalpinia sappan*. *Biosci Biotechnol Biochem*. 2013;77(12):2378-2382.
31. Zhao M-B, Li J, Shi S-P, et al. Two new phenolic compounds from the heartwood of *Caesalpinia sappan* L. *Molecules*. 2014;19(1):1-8.
32. Wang Z, Sun J-B, Qu W, Guan F-Q, Li L-Z, Liang J-Y. Caesappin A and B, two novel protosappanins from *Caesalpinia sappan* L. *Fitoterapia*. 2014;92:280-284.
33. Calvo MI. Homoisoflavanones from *Ledebouria floribunda*. *Fitoterapia*. 2009;80(2):96-101.
34. H-B H, Zhu J-H. Flavonoid constituents from the roots of *Acanthopanax brachypus*. *Chem Pharm Bull*. 2011;59(1):135-139.
35. Kosar S, Fatima I, Mahmood A, et al. Purunusides A-C, α-glucosidase inhibitory homoisoflavone glucosides from *Prunus domestica*. *Arch Pharm Res*. 2009;32(12):1705-1710.
36. Calvo MI. Three new homoisoflavanones from the bulbs of *Ledebouria floribunda*. *Fitoterapia*. 2009;80(7):394-398.
37. Zhao H, Bai H, Wang Y, Li W, Koike K. A new homoisoflavan from *Caesalpinia sappan*. *J Nat Med*. 2008;62(3):325-327.
38. DY H, YP L, Tang HB, et al. Phenolic compounds from the twigs and leaves of Tara (*Caesalpinia spinosa)*. *J Asian Nat Prod Res*. 2016;18(4):334-338.
39. Dutra-Behrens M, Schmeda-Hirschmann G. New homoisoflavanes, a new alkaloid and spirostane steroids from the roots of *Herreria montevidensis* Klotzsch ex Griseb. (Herreriaceae. *Molecules*. 2016;21(11):E1589.
40. Awale S, Miyamoto T, Linn TZ, et al. Cytotoxic constituents of *Soymida febrifuga* from Myanmar. *J Nat Prod*. 2009;72(9):1631-1636.
41. Youn UJ, Lee YS, Jeong H, et al. Identification of antiadipogenic constituents of the rhizomes of *Anemarrhena asphodeloides*. *J Nat Prod*. 2009;72(10):1895-1898.
42. Li M-C, Yao Z, Takaishi Y, Tang S-A, Duan H-Q. Isolation of novel phenolic compounds with multidrug resistance (MDR) reversal properties from *Onychium japonicum*. *Chem Biodivers*. 2011;8(6):1112-1120.
43. Zhao H, Wang X, Li W, Koike K, Bai H. A new minor homoisoflavonoid from *Caesalpinia sappan*. *Nat Prod Res*. 2014;28(2):102-105.
44. LC F, Huang X, Lai ZY, YJ H, Liu HJ, Cai XL. A new 3-benzylchroman derivative from sappan Lignum (*Caesalpinia sappan)*. *Molecules*. 2008;13(8):1923-1930.
45. Jeong HJ, Kim YM, Kim JH, et al. Homoisoflavonoids from *Caesalpinia sappan* displaying viral neuraminidases inhibition. *Biol Pharm Bull*. 2012;35(5):786-790.
46. Dai Y, Harinantenaina L, Brodie PJ, et al. Antiproliferative homoisoflavonoids and bufatrienolides from *Urginea depressa*. *J Nat Prod*. 2013;76(5):865-872.
47. Chen H, Li Y-J, Li X-F, et al. Homoisoflavanones with estrogenic activity from the rhizomes of *Polygonatum sibiricum*. *J Asian Nat Prod Res*. 2018;20(1):92-100.
48. Yan J, Sun L-R, Zhou Z-Y, et al. Homoisoflavonoids from the medicinal plant *Portulaca oleracea*. *Phytochemistry*. 2012;80:37-41.
49. Tsai Y-C, Chiang S-Y, El-Shazly M, et al. The oestrogenic and anti-platelet activities of dihydrobenzofuroisocoumarins and homoisoflavonoids from *Liriope platyphylla* roots. *Food Chem*. 2013;140(1-2):305-314.
50. Zhou X, Yuping Z, Zhao H, Liang J, Zhang Y, Shi S. Antioxidant homoisoflavonoids from *Polygonatum odoratum*. *Food Chem*. 2015;186:63-68.
51. Tchegnitegni BT, Teponno RB, Tanaka C, Gabriel AF, Tapondjou LA, Miyamoto T. Sappanin-type homoisoflavonoids from *Sansevieria trifasciata* Prain. *Phytochem Lett*. 2015;12:262-266.
52. Ata A, Gale EM, Samarasekera R. Bioactive chemical constituents of *Caesalpinia bonduc* (Fabaceae). *Phytochem Lett*. 2009;2(3):106-109.
53. Schwikkard SL, Whitmore H, Corson TW, et al. Antiangiogenic activity and cytotoxicity of triterpenoids and homoisoflavonoids from *Massonia pustulata* and *Massonia bifolia*. *Planta Med*. 2018;84(9-10):638-644.
54. El-Elimat T, Rivera-Chávez J, Burdette JE, et al. Cytotoxic homoisoflavonoids from the bulbs of *Bellevalia flexuosa*. *Fitoterapia*. 2018;127:201-206.
55. Schwikkard S, Alqahtani A, Knirsch W, et al. Phytochemical investigations of three *Rhodocodon* (Hyacinthaceae Sensu APG II) species. *J Nat Prod*. 2017;80(1):30-37.
56. Bezabih M, Famuyiwa SO, Abegaz BM. HPLC analysis and NMR identification of homoisoflavonoids and stilbenoids from the inter-bulb surfaces of *Scilla nervosa*. *Nat Prod Commun*. 2009;4(10):1367-1370.
57. Matsuo Y, Kurihara R, Akagi N, Mimaki Y. Two new homoisoflavonoids from the bulbs of *Bessera elegans*. *Nat Prod Commun*. 2014;9(12):1725-1727.

58. Li L-M, Yuan Q-P, Chen G. Four homoisoflavonoids isolated from traditional Chinese medicine: "gan luo xin". *J Asian Nat Prod Res*. 2014;16(8):813-818.
59. Gan L-S, Chen J-J, Shi M-F, Zhou C-X. A new homoisoflavanone from the rhizomes of *Polygonatum cyrtonema*. *Nat Prod Commun*. 2013;8(5):597-598.
60. Zhang H, Yang F, Qi J, et al. Homoisoflavonoids from the fibrous roots of *Polygonatum odoratum* with glucose uptake-stimulatory activity in 3T3-L1 adipocytes. *J Nat Prod*. 2010;73(4):548-552.
61. Wang W, Dabu X, He J, et al. Polygonatone H, a new homoisoflavanone with cytotoxicity from *Polygonatum Cyrtonema* Hua. *Nat Prod Res*. 2018;46:1-7.
62. Nishida Y, Eto M, Miyashita H, et al. A new homostilbene and two new homoisoflavones from the bulbs of *Scilla scilloides*. *Chem Pharm Bull*. 2008;56(7):1022-1025.
63. Alali F, El-Elimat T, Albataineh H, et al. Cytotoxic homoisoflavones from the bulbs of *Bellevalia eigii*. *J Nat Prod*. 2015;78(7):1708-1715.
64. Hafez Ghoran S, Saeidnia S, Babaei E, et al. Biochemical and biophysical properties of a novel homoisoflavonoid extracted from *Scilla persica* HAUSSKN. *Bioorg Chem*. 2014;57:51-56.
65. Wang D, Li D, Zhu W, Peng P. A new C-methylated homoisoflavanone and triterpenoid from the rhizomes of *Polygonatum odoratum*. *Nat Prod Res*. 2009;23(6):580-589.
66. Cuong TD, Hung TM, Kim JC, et al. Phenolic compounds from *Caesalpinia sappan* heartwood and their anti-inflammatory activity. *J Nat Prod*. 2012;75(12):2069-2075.
67. Liu J, Mei W-L, Wu J, Zhao Y-X, Peng M, Dai H-F. A new cytotoxic homoisoflavonoid from *Dracaena cambodiana*. *J Asian Nat Prod Res*. 2009;11(2):192-195.
68. Xu S, Shang M-Y, Liu G-X, et al. Chemical constituents from the rhizomes of *Smilax glabra* and their antimicrobial activity. *Molecules*. 2013;18(5):5265-5287.
69. Koorbanally C, Sewjee S, Mulholland DA, Crouch NR, Dold A. Homoisoflavanones from *Pseudoprospero firmifolium* of the monotypic tribe Pseudoprospereae (Hyacinthaceae: Hyacinthoideae). *Phytochemistry*. 2007;68(22-24):2753-2756.
70. Tantray MA, Shawl AS, Khuroo MA, Ali N. Homoisoflavanones from *Lespedeza juncea*. *Chem Nat Compd*. 2008;44(4):424-426.
71. Roy SK, Agrahari UC, Gautam R, Srivastava A, Jachak SM, Isointricatinol JSM. Isointricatinol, a new antioxidant homoisoflavonoid from the roots of *Caesalpinia digyna* Rottler. *Nat Prod Res*. 2012;26(8):690-695.
72. Chen P, Yang J-S. Flavonol galactoside caffeiate ester and homoisoflavones from *Caesalpinia millettii* HOOK. et ARN. *Chem Pharm Bull*. 2007;55(4):655-657.
73. Maheswara M, Siddaiah V, Venkata Rao C, Rao C. Two new homoisoflavonoids from *Caesalpinia pulcherrima*. *Chem Pharm Bull*. 2006;54(8):1193-1195.
74. Das B, Thirupathi P, Ravikanth B, Aravind Kumar R, Sarma AVS, Basha SJ. Isolation, synthesis, and bioactivity of homoisoflavonoids from *Caesalpinia pulcherrima*. *Chem Pharm Bull*. 2009;57(10):1139-1141.
75. Waller CP, Thumser AE, Langat MK, Crouch NR, Mulholland DA. COX-2 inhibitory activity of homoisoflavanones and xanthones from the bulbs of the southern African *Ledebouria socialis* and *Ledebouria ovatifolia* (Hyacinthaceae: Hyacinthoideae). *Phytochemistry*. 2013;95:284-290.
76. Che Y-Y, Qian Y, Wu Y, Wei-Qu , Liang J-Y. Two new Homoisoflavanones from the rhizome of Polygonatum odoratum. *Chem Nat Compd*. 2015;51(1):54-56.
77. Koorbanally C, Crouch NR, Langlois A, Du Toit K, Mulholland DA, Drewes SE. Homoisoflavanones and spirocyclic nortriterpenoids from three *Eucomis* species: *E. comosa, E. schijffii* and *E. pallidiflora* subsp. *pole-evansii* (Hyacinthaceae). *South Afr J Bot*. 2006;72(3):428-433.
78. Hafez Ghoran S, Saeidnia S, Babaei E, Kiuchi F, Hussain H. Scillapersicene: a new homoisoflavonoid with cytotoxic activity from the bulbs of *Scilla persica* HAUSSKN. *Nat Prod Res*. 2016;30(11):1309-1314.
79. Ngamga D, Bipa J, Lebatha P, et al. Isoquinoline alkaloids and homoisoflavonoids from *Drimiopsis barteri* Bak and *D. burkei* Bak. *Nat Prod Commun*. 2008;3(5):769-777.
80. Xu H-X, Lee SF. The antibacterial principle of *Caesalpina sappan*. *Phytother Res*. 2004;18(8):647-651.
81. Lee EB, Xing MM, Kim DK. Lifespan-extending and stress resistance properties of Brazilin from *Caesalpinia sappan* in *Caenorhabditis elegans*. *Arch Pharm Res*. 2017;40(7):825-835.
82. Batubara I, Mitsunaga T, Ohashi H. Brazilin from *Caesalpinia sappan* wood as an antiacne agent. *J Wood Sci*. 2010;56(1):77-81.
83. Lee S, Choi S-Y, Choo Y-Y, et al. Sappanone A exhibits anti-inflammatory effects via modulation of Nrf2 and NF-κB. *Int Immunopharmacol*. 2015;28(1):328-336.
84. Rivero-Cruz JF. Antimicrobial compounds isolated from *Haematoxylon brasiletto*. *J Ethnopharmacol*. 2008;119(1):99-103.
85. Wang H, Fowler MI, Messenger DJ, et al. Homoisoflavonoids are potent glucose transporter 2 (GLUT2) inhibitors: a potential mechanism for the glucose-lowering properties of *Polygonatum odoratum*. *J Agric Food Chem*. 2018;66(12):3137-3145.
86. Guo H, Zhao H, Kanno Y, et al. A dihydrochalcone and several homoisoflavonoids from *Polygonatum odoratum* are activators of adenosine monophosphate-activated protein kinase. *Bioorg Med Chem Lett*. 2013;23(11):3137-3139.
87. Lin H-R. Two homoisoflavonoids act as peroxisome proliferator-activated receptor agonists. *Med Chem Res*. 2015;24(7):2898-2905.
88. Uesawa Y, Sakagami H, Kagaya H, Yamashita M, Takao K, Sugita Y. Quantitative structure-cytotoxicity relationship of 3-benzylidenechromanones. *Anticancer Res*. 2016;36(11):5803-5812.

89. Singh VK, Arora D, Satija NK, Khare P, Roy SK, Sharma PK. Intricatinol synergistically enhances the anticancerous activity of cisplatin in human A549 cells via p38 MAPK/p53 signalling. *Apoptosis*. 2017;22(10):1273-1286.
90. Lin L-G, Xie H, Li H-L, et al. Naturally occurring homoisoflavonoids function as potent protein tyrosine kinase inhibitors by c-Src-based high-throughput screening. *J Med Chem*. 2008;51(15):4419-4429.
91. Lin L-G, Xie H, Wang Y-T, Ding J, Ye Y. Chemical constituents from the heartwood of *Haematoxylon campechianum* as protein tyrosine kinase inhibitors. *Chem Biodivers*. 2014;11(5):776-783.
92. Liang C-H, Chan L-P, Chou T-H, et al. Brazilein from *Caesalpinia sappan* L. Antioxidant inhibits adipocyte differentiation and induces apoptosis through caspase-3 activity and anthelmintic activities against *Hymenolepis nana* and *Anisakis simplex*. *Evid Based Complement Alternat Med*. 2013;2013(6):864892
93. Yang X, Ren L, Zhang S, Zhao L, Wang J. Antitumor effects of purified protosappanin B extracted from *Lignum Sappan*. *Integr Cancer Ther*. 2016;15(1):87-95.
94. Shim JS, Kim JH, Lee J, Kim SN, Kwon HJ. Anti-angiogenic activity of a homoisoflavanone from *Cremastra appendiculata*. *Planta Med*. 2004;70(2):171-173.
95. Amin SA, Adhikari N, Gayen S, Jha T. Homoisoflavonoids as potential antiangiogenic agents for retinal neovascularization. *Biomed Pharmacother*. 2017;95:818-827.
96. Basavarajappa HD, Lee B, Lee H, et al. Synthesis and biological evaluation of novel homoisoflavonoids for retinal neovascularization. *J Med Chem*. 2015;58(12):5015-5027.
97. Lin M, Sun W, Gong W, Zhou Z, Ding Y, Hou Q. Methylophiopogonanone A protects against cerebral ischemia/reperfusion injury and attenuates blood−brain barrier disruption in vitro. *PLoS One*. 2015;10(4):1-14.
98. Lin Y-F, Fong C, Peng W-L, Tang K-C, Liang Y-E, Li W-T. Synthesis of 3-(2-olefinbenzyl)-4H-chromen-4-one through cyclobenzylation and catalytic C-H bond functionalization using palladium (II). *J Org Chem*. 2017;82(20):10855-10865.
99. Raja GCE, Ryu JY, Lee J, Lee S. Ruthenium-catalyzed C-H activation of salicylaldehyde and decarboxylative coupling of alkynoic acids for the selective synthesis of homoisoflavonoids and flavones. *Org Lett*. 2017;19(24):6606-6609.
100. Devarajan K, Devaraj S, Balasubramanian KK, Bhagavathy S. An unexpected thermal [1,3]-[1,3]- para rearrangement of chromone-3-ylmethyl aryl ethers: mechanism and application of the intercepted [1,3]-rearranged intermediates to the synthesis of cis-homopterocarpans. *Chem Lett*. 2015;44(4):551-553.
101. Tinto WF, Simmons-Boyce JL, McLean S, Reynolds WF. Constituents of *Agave americana* and *Agave barbadensis.* *Fitoterapia*. 2005;76(6):594-597.
102. Y-C Y, Zhu S, X-W L, Wu Y, Liu B. Enantioselective synthesis of four natural homoisoflavonoids. *Eur J Organ Chem*. 2015;2015(22):4964-4972.
103. Camarda L. Merlini l, Nasini G. Dragon's blood from *Dracaena draco*, Structure of novel homoisoflavonoids. *Heterocycles*. 1983;20(1):39-43.
104. Singh DK, Jung Y, Kim I. Total syntheses of urgineanins A, B, D, and their analogues. *Synthesis*. 2017;49(7):1531-1537.
105. Boehler P, Tamm C. The homo-isoflavones, a new class of natural product. Isolation and structure of eucomin and eucomol. *Tetrahedron Lett*. 1967;8(36):3479-3483.
106. Krawczyk E, Koprowski M, Mielniczak G, Owsianik K. Symmetric synthesis of 5,7-*O*-dimethyleucomols via enantioselective oxidation of enol phosphates. *Tetrahedron Asymmetry*. 2015;26(15-16):876-883.
107. Takikawa H, Suzuki K. Modified chiral triazolium salts for enantioselective benzoin cyclization of enolizable keto-aldehydes: Synthesis of (+)-sappanone B. *Organ Lett*. 2007;9(14):2713-2716.
108. Yen CT, Nakagawa-Goto K, Hwang TL, et al. Antitumor agents. 271: total synthesis and evaluation of brazilein and analogs as anti-inflammatory and cytotoxic agents. *Bioorg Med Chem Lett*. 2010;20(3):1037-1039.
109. Yadav JS, Mishra AK, Das S. Formal synthesis of (±)-brazilin and total synthesis of (±)-brazilane. *Tetrahedron*. 2014;70(41):7560-7566.
110. Wang X, Zhang H, Yang X, Zhao J, Pan C. Enantioselective total synthesis of (+)-brazilin, (−)-brazilein and (+)-brazilide A. *Chem Commun*. 2013;49(47):5405-5407.
111. Devarajan K, Devaraj S, Balasubramanian KK, Bhagavathy S. An unexpected thermal [1,3]-[1,3]- *para* rearrangement of chromone-3-ylmethyl aryl ethers: mechanism and application of the intercepted [1,3]-rearranged intermediates to the synthesis of *cis* -homopterocarpans. *Chem Lett*. 2015;44(4):551-553.